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*The National Professional Society of Pharmacists*

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Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket 02D-0242

Dear Sir/Madam:

The American Pharmaceutical Association (APhA) welcomes the opportunity to submit comments on the Food and Drug Administration's (FDA) Compliance Policy Guide Manual entitled "Sec. 460.200 Pharmacy Compounding." APhA, the national professional society of pharmacists, represents more than 50,000 practicing pharmacists, pharmaceutical scientists, student pharmacists, and pharmacy technicians.

APhA has significant concerns with the Pharmacy Compounding Compliance Policy Guide (CPG) released in June 2002. APhA's concerns include the Agency's decision to revert to its pre-Food and Drug Administration Modernization Act of 1997 (FDAMA) position on pharmacy compounding, the development and release of the Compliance Policy Guide without collaboration with the pharmacy profession or state regulatory agencies, and the factors identified to distinguish between traditional pharmacy compounding and manufacturing.

The practice of compounding is an important and long-standing component of the pharmacy profession. Compounding occurs when a drug is prepared through the combining, mixing or putting together of two or more ingredients or components by a pharmacist pursuant to, or in anticipation of, a prescription order. Compounding has always been a basic part of pharmacy practice. The early practice of pharmacy required the compounding of virtually all medications, because there were few, if any, commercially available products. As pharmaceutical companies were founded there became less need for compounding widely used products, although the need to compound has certainly not disappeared. Today, pharmacists compound alternatives to commercially available products or modify a manufactured product by, for example, adjusting the dose, changing the form of the drug (e.g., tablet to a liquid), or preparing an alternative without offending preservatives, dyes, or allergens.

Compounding allows a pharmacist to create a medication tailored to an individual patient's needs. Pharmacists use their medication knowledge and expertise to produce individualized medications that meet these needs and improve health outcomes. Without

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compounding, many patients would not have access to the correct combination of ingredients, the appropriate dose and dosage form, or the best delivery system. Other medications must be compounded because they do not have sufficient shelf life to withstand the commercial distribution process and must be prepared at the time of dispensing. The practice of compounding is a traditional part of pharmacy practice and a fundamental responsibility of the profession.

***FDA's Position on Pharmacy Compounding***

The Federal Food, Drug, and Cosmetic Act of 1938 (FDCA) was created to regulate drug manufacturing, marketing, and distribution. The Act was not aimed at regulating compounding pharmacies or pharmacy practice, but at manufacturers. For nearly 50 years after the passage of the Act, the FDA did not seek to regulate compounding pharmacists, but left this regulation to the States.[1] However, in March 1992, the FDA issued a Compliance Policy Guide (7132.16) in an attempt to regulate pharmacy compounding. Some components of the CPG, as well as several parts of the National Association of Boards of Pharmacy (NABP) Model Rules, were eventually codified into the Food and Drug Administration Modernization Act of 1997 (FDAMA). FDAMA reinforced the legitimacy of pharmacy compounding and clarified the inapplicability of the FDCA to compounding.[2]

Prior to the enactment of FDAMA, when the Agency promulgated its 1992 CPG, the FDA claimed that compounded drugs were subject to certain provisions of the FDCA:

> "It should be noted, however, that while retail pharmacies that meet the statutory requirements of the Federal Food, Drug, and Cosmetic Act (Act), they are not the subject of any general exemption from the new drug, adulteration, or misbranding provisions of the Act."[3]

The Agency implied, as it did again in its Petitioners Brief in Thompson v. Western States Medical Center, that compounding equates to the manufacturing of new drugs, and that compounding without a New Drug Application (NDA) or Investigational New Drug Application (IND) is illegal. This is an interpretation of the law that Congress clearly did not agree with as seen in the enactment of FDAMA. Compounding of drug products by pharmacists and physicians does not constitute the manufacturing of "new drugs."

In April 2002, the Supreme Court declared Section 503A (the pharmacy compounding section) of FDAMA invalid finding the law's advertising restrictions a violation of the First Amendment.[4] While the Court declared the advertising restrictions unconstitutional, the

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[1] Thompson v. Western States Medical Center, 122 S.Ct. 1497 (2002).
[2] S. Rep. No. 43, 105th Cong., 1st Sess., 67-68 (1997).
[3] Food and Drug Administration. "Background." Compliance Policy Guides: Chapter 32 – Drugs General (7132.16). March 16, 1992. Pg. 1.
[4] Thompson v. Western States Medical Center, 122 S.Ct. 1497 (2002).

Court did not address whether this provision was severable from the law. The Court invalidated the pharmacy compounding section of FDAMA only because of the flawed advertising restrictions, not because it examined and found substantial problems with the remainder of the law. It is therefore inappropriate that the FDA use the Court's decision to revert back to its pre-FDAMA position on pharmacy compounding. If the FDA felt the need to issue guidance in light of the Court's decision, the Agency should have incorporated the compounding provisions in FDAMA into a new guidance document. Instead, the Agency responded to the Court's decision by reissuing its 1992 CPG, which is substantially more restrictive than FDAMA, with just a few minor modifications. The intentions of Congress remain clear – compounding is a traditional part of pharmacy practice that does not violate the FDCA.

APhA is disappointed that the Agency chose to release a new Compliance Policy Guide in the manner and with the content it did. With the exception of the deletion of the soliciting business restriction and a few minor word changes, Compliance Policy Guide "Sec. 460.200 Pharmacy Compounding" is almost identical to the 1992 CPG. The new CPG attempts to assert the FDA's authority to take enforcement actions related to compounding. The CPG states that the "FDA is considering the implications of that decision [Thompson v. Western States] and determining *how it intends to regulate pharmacy compounding in the long term*" [emphasis added].[5] We do not believe that the FDA should be considering how it "intends to regulate pharmacy compounding." The FDA has been empowered by Congress to regulate the *manufacturing* of pharmaceuticals, but the regulation of pharmacy practice—and of compounding—remains a state function. Historically, state boards of pharmacy have regulated pharmacists and pharmacy practice. We are not aware of any legislation that has granted the Agency authority over pharmacy practice or the state boards, and the profession is not prepared to defer to the Agency on issues of pharmacy practice.

***The Development and Release of the CPG***

According to the Agency, the Pharmacy Compounding Compliance Policy Guide was issued to provide "guidance to drug compounders and the staff of the FDA on how the Agency intends to address pharmacy compounding of human drugs in the immediate future as a result of the decision of the Supreme Court in Thompson v. Western States Medical Center."[6] The CPG was developed by the Agency and issued without the benefit of receiving public comment. As explained in the June 7, 2002 *Federal Register* Notice announcing the availability of the guidance document, the CPG was "implemented immediately without prior public comment... because of the agency's urgent need to explain how, in light of the Supreme Court decision, it will exercise its enforcement discretion in regard to compounded human drugs."[7]

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[5] Food and Drug Administration. "Introduction." Compliance Policy Guides Manual: Sec. 460.200 Pharmacy Compounding. May 2002. Pg. 1.

[6] Ibid., Pg. 1.

[7] 67 FR at 39,410.

We do not agree that there was an "urgent need" for the FDA to issue guidance on pharmacy compounding. As previously stated, the FDA is not responsible for regulating the practice of pharmacy. State boards of pharmacy continue to regulate the pharmacy profession. The invalidation of the compounding provisions of FDAMA did not alter states' ability to regulate the profession. Also, states within the Ninth Circuit Court's jurisdiction have been operating without Section 503A since the U.S. Court of Appeals declared the entire pharmacy compounding section invalid in February 2001. The remainder of the country operated without the benefit of the compounding section of FDAMA for more than two months before the Agency released the CPG. Clearly there was no pressing need for the Agency to take action without first seeking public comment.

Public comment would have allowed the Agency to initiate a collaborative effort with pharmacists, state boards of pharmacy, and other interested parties. By issuing the CPG without public comment, the FDA is operating contrary to its stated goals of working in a cooperative manner, and soliciting meaningful feedback from interested parties. Soliciting comments after the Compliance Policy Guide was released and implemented does not provide the public with an opportunity to shape the development of the document; and it is not an acceptable substitute. In addition, soliciting public comment prior to the document's release would have allowed interested parties to identify areas of concern or confusion with the CPG. The FDA could have addressed those areas *prior* to the guidance's implementation.

If the Agency felt time constraints prevented the solicitation of public comments, the FDA did have another mechanism to obtain feedback from the pharmacy community—the Agency's Pharmacy Compounding Advisory Committee. It is our understanding that the Agency did not share the CPG with the Advisory Committee before its release.

***Factors to Distinguish Between Compounding and Manufacturing***

According to the Compliance Policy Guide, the FDA will consider enforcement action against a pharmacist/pharmacy when the scope and nature of activities raise the kind of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA.[8] The CPG contains nine factors that the FDA will consider when determining whether to initiate enforcement action. The factors are intended to help the Agency distinguish compounding from manufacturing. APhA is concerned that several of the factors do not appear to address manufacturing, but rather address safety issues and good compounding practices. It is unclear how factors related to good compounding practices can be used to determine if an entity is acting as a manufacturer. An alternative approach would have the Agency define what constitutes manufacturing, rather than trying to develop factors that describe what falls within traditional pharmacy compounding. The FDA does not have the authority to set or measure compounding safety standards. This authority continues to rest with the state boards of pharmacy, and other standard setting organizations such as the U.S. Pharmacopoeia (USP).

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[8] Food and Drug Administration. "Policy." Compliance Policy Guides Manual: Sec. 460.200 Pharmacy Compounding. May 2002. Pg. 3.

APhA is also concerned that several of the factors are vague and ambiguous in nature. For example, Factor 1 uses the terminology "very limited quantities." The term "very limited quantities" is not defined or explained. What pharmacists consider "very limited quantities" will differ, and may differ from the Agency's view. Without defining or clarifying some of the vague and ambiguous terms, we can expect differences of opinion among FDA inspectors and between them and the pharmacists' practices they are inspecting. It will be impossible for pharmacists to feel secure in the knowledge that they will not be investigated as potential manufacturers when there is no clear understanding of the factors listed in the CPG. A pharmacist's ability to operate within the guidelines is further complicated when one considers that the FDA has reserved the right to consider additional factors not listed in the guidance document on a case by case basis. "The... list of factors is not intended to be exhaustive. Other factors may be appropriate for consideration" when determining to take enforcement action.[9]

APhA has additional specific concerns with the nine factors listed in the CPG. Those concerns are addressed individually below.

*Factor 1: Compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions.*[10]
This factor is a significant departure from the FDA's position in the 1992 Compliance Policy Guide. The 1992 CPG stated that pharmacists or physicians should not compound "*inordinate amounts* of drugs in anticipation of receiving prescriptions in relation to the amounts of drugs compounded after receiving valid prescriptions."[11] Although the terminology "inordinate amounts" was not well-defined in the 1992 CPG, there was a general understanding that the Agency would consider enforcement action if a pharmacy compounded excessive amounts of drug products in relation to the number of prescriptions that could be reasonably anticipated based on past history. The 2002 CPG terminology is also a departure from the language contained in the compounding section of FDAMA which allowed compounding in "*limited quantities* before the receipt of a valid prescription." The Agency's change from "inordinate amounts" and "limited quantities" to "*very limited* quantities" in the 2002 CPG is much more restrictive.

As previously mentioned above, the term "very limited quantities" is also vague and ambiguous and subject to interpretation by health care providers and the Agency. Depending on the interpretation by the Agency, any pharmacist that compounds a drug product in anticipation of a prescription could be subject to enforcement action.

Instead of setting arbitrary limits on prescription compounding, APhA recommends that the FDA revise the factor to allow for advance compounding based on the quantity

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[9] Food and Drug Administration. "Policy." Compliance Policy Guides Manual: Sec. 460.200 Pharmacy Compounding. May 2002. Pg. 4.
[10] Ibid., Pg. 3.
[11] Food and Drug Administration. "Policy." Compliance Policy Guides: Chapter 32 – Drugs General (7132.16). March 16, 1992. Pg. 5.

historically prescribed and dispensed, the stability of the preparation, and the assigned beyond-use date. It is not unreasonable for pharmacists to compound drug products in advance in anticipation of patient refills and physician prescribing patterns. Advance compounding is not an indicator of manufacturing.

Advance compounding may also improve patient safety. For some products that must be tested for sterility, such as sterile injectables, it may be anywhere from four days to two weeks to obtain final results. Advance preparation allows the pharmacist adequate time to have the product tested before it is dispensed to the patient. In these situations, advance preparation of the product is the only way to dispense a quality, tested product to the patient without untimely delays.

*Factor 2: Compounding drugs that were withdrawn or removed from the market for safety reasons.*[12]

APhA generally agrees with the premise behind Factor 2 – drug products that have been proven unsafe should not be compounded or dispensed to patients. This factor, which was initially included in FDAMA, relies on the creation and publication of a list of such drugs by the FDA. APhA requests that the Agency identify and allow public comment before it adds new drug products to the list of compounding drugs that were withdrawn or removed from the market for safety reasons. Public comment will help ensure that the appropriate drug products are added to the "do not compound" list. APhA is concerned that drug products could be added to list not because they were proven unsafe, but because they were withdrawn for absence of safety information because the manufacturer chooses not to research and provide such information for a low revenue product. It is important that valuable drug therapies are not removed from health care providers' therapeutic arsenal solely for financial reasons.

While the CPG clearly states that the guidance document is applicable to the "compounding of human drugs," some of the Association's members are concerned with the potential effects it could have on veterinary compounding. For example, many veterinarians prescribe compounded drug products containing ingredients that have been withdrawn for human use. While the use of these ingredients in non-human prescriptions should not trigger enforcement action by the FDA, we are concerned that the inclusion of these products on the pharmacy's supply list could be misconstrued by FDA investigators reviewing a pharmacy's supply records.

APhA is also concerned that this factor is included among factors used to distinguish manufacturing from compounding. As previously stated, although APhA generally agrees with this factor, we do not see how the use of drug products that have been removed from the market for safety reasons is in any way indicative of pharmaceutical manufacturing. Instead of distinguishing manufacturing from compounding, it appears that this factor is

[12] Food and Drug Administration. "Policy." Compliance Policy Guides: Chapter 32 – Drugs General (7132.16). March 16, 1992. Pg. 5.

related to compounding safety issues—an area that is regulated by the states. Many states already prohibit the compounding of any drug that the FDA has identified as withdrawn or removed from the market for safety reasons. APhA suggests that the Agency encourage state boards of pharmacy to include this restriction in their regulations if they have not already done so.

*Factor 3: Compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs without an FDA sanctioned investigational new drug application (IND) in accordance with 21 U.S.C. § 355(i) and 21 CFR 312.*[13]
As with Factor 2, this factor addresses the types of ingredients that may or may not be used to compound drug products. APhA reiterates its belief that compounded drug product ingredients should have no bearing on efforts to distinguish manufacturing from traditional compounding. The Agency should defer to state boards of pharmacy for the regulation of good compounding practices.

APhA is also concerned that this factor is much more restrictive than related language found in FDAMA. FDAMA listed three sources of bulk drug ingredients that could be used in compounding: drug substances that are components of drugs approved by the Secretary, drug substances that comply with the standards of an applicable U.S. Pharmacopoeia or National Formulary monograph (if a monograph exists), and/or drug substances that appear on a list developed by the Secretary.[14] The new CPG reduces the number of potential sources for bulk drug products from three to one. The CPG would only allow the use of bulk drug products that are components of FDA approved drugs.[15]

The current language of this factor appears to preclude many currently compounded drug products. For example, the factor fails to address drugs on the market from before 1938, and thus not FDA-approved. Pharmacists would no longer be able to compound drug products that include commonly used ingredients for which there is no New Drug Application and no listing in the FDA Orange Book, the Agency's listing of approved drug substances. An examination of the Orange Book by the International Academy of Compounding Pharmacists (IACP) found numerous commonly used drug substances that are not included in the Orange Book such as chloral hydrate, estriol, histamine diphosphate, and phenobarbital.[16]

APhA recommends that the FDA eliminate this factor from the CPG. As with the previous factor addressing the compounding of drugs that were withdrawn or removed from the market for safety reasons, many state regulations already denote acceptable bulk drug substances and the Agency should encourage other states to follow suit.

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[13] Food and Drug Administration. "Policy." Compliance Policy Guides: Chapter 32 – Drugs General (7132.16). March 16, 1992. Pg. 4.
[14] FDCA § 503A(b)(i)(II).
[15] Food and Drug Administration. "Policy." Compliance Policy Guides: Chapter 32 – Drugs General (7132.16). March 16, 1992. Pg. 4.
[16] International Academy of Compounding Pharmacists. "Comments to the FDA on Docket No. 02D-0242." August 5, 2002. Pg. 14.

If the Agency maintains this factor in the CPG, the Agency should, at a minimum, reinstate the three sources of bulk drug ingredients. As required by FDAMA, the FDA has already developed a list of acceptable bulk drug substances that are not components of FDA-approved drugs and do not have a USP monograph. The Agency could easily revise the factor to reinstate this list and acknowledge that bulk drug substances with USP or NF monographs are suitable for compounding. Since FDAMA was enacted five years ago, compounders have been using all three of these sources for active bulk drug ingredients. There is no apparent reason why the FDA-approved list and USP and NF monographs should be disallowed now.

Limiting bulk drug ingredients to drugs that are components of FDA-approved drug products greatly limits the number of ingredients that can be used to prepare compounded medications, and reduces pharmacists' and physicians' ability to provide their patients with medications tailored to their individual needs.

*Factor 4: Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility.*[17]
This requirement would require pharmacists to obtain written assurance from each manufacturer/supplier of drug substances that it was manufactured in a FDA-registered facility. FDAMA provided for the use of bulk drug products that are manufactured by an establishment registered as a manufacturer under Section 510, or as a foreign manufacturer under Section 510(i), however, pharmacists were not required to obtain written proof of the manufacturer's registration.[18] Pharmacists are not in the position to act as an arm of the Agency and ensure that other entities have met FDA requirements. Also, as discussed in Factors 2 and 3, this factor concerns the types of ingredients used in pharmacy compounding. This factor cannot be reasonably used to identify manufacturing entities masquerading as compounding pharmacies.

This factor would create an unjustified administrative burden for both pharmacies and the manufacturers/suppliers of drug substances. APhA has learned from several manufacturers/suppliers of bulk drug ingredients that they do not currently provide written proof of manufacture in a FDA-approved facility. One supplier indicated that a requirement to start providing this written assurance would be so burdensome that it would be less likely to sell to compounders—particularly pharmacies that utilize smaller amounts of drug substances. APhA suggests that the Agency revise the factor to require suppliers to instead provide a warning if the drug substance was not manufactured in a FDA-approved facility.

This factor also creates several unanswered questions. The factor requires that pharmacies receive written assurance "from the supplier." In this situation who qualifies as the

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[17] Food and Drug Administration. "Policy." Compliance Policy Guides Manual: Sec. 460.200 Pharmacy Compounding. May 2002. Pg. 4.
[18] FDCA § 503(b)(1)(A)(ii).

"supplier"? Can the pharmacy obtain the written assurance from the wholesaler or importer that sells directly to the pharmacy? Or must the written assurance be obtained from the original manufacturer—an entity with whom most pharmacies do not have direct contact. APhA recommends that this factor be clarified to state that documentation may be obtained from the pharmacy's immediate supplier. APhA further recommends that the FDA revise the factor to remove the written assurance requirement for drug substances that are USP, NF, certified American Chemical Society (ACS), or Food Chemicals Codex (FCC) grade; or for substances accompanied by a certificate of analysis for quality documentation.

The factor also requires that pharmacists not receive, store, or use drug substances "*without first obtaining* written assurance." Does this factor require pharmacies to obtain written assurance from the supplier *before* taking receipt of the drug substance? If so, this requirement could create untimely delays for patients in need of a medication compounded from one of these drug substances. APhA requests that the Agency clarify this factor by removing the word "first" and making a list of registered facilities readily available to pharmacists.

*Factor 5: Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements.*[19]
Again as with Factors 2, 3, and 4, this factor addresses drug substances that may or may not be used in compounding. As previously stated, these factors should be removed from the CPG as they do not relate to the identification of pharmaceutical manufacturers.

This factor restricts the use of ingredients to only those that meet official compendia requirements such as USP or NF monographs. While APhA agrees that pharmacists should utilize USP or NF grade ingredients when a USP or NF monograph exists, limiting compounding to only those ingredients would dramatically reduce the number of drug components available. A large number of drug components do not have compendia requirements.

APhA recommends that the FDA clarify that this factor only applies to drug components that have USP monographs and does not apply to inactive ingredients such as excipients. The factor could be revised by inserting language contained in FDAMA:

> "Receiving, storing, or using drug components not guaranteed or otherwise determined to *comply with the standards of an applicable Unites States Pharmacopoeia or National Formulary monograph, if a monograph exists.*"

[19] Food and Drug Administration. "Policy." Compliance Policy Guides Manual: Sec. 460.200 Pharmacy Compounding. May 2002. Pg. 4.

*Factor 6: Using commercial scale manufacturing or testing equipment for compounding drug products.*[20]

This factor examines the use of commercial scale manufacturing and testing equipment. While APhA understands that the Agency is concerned that individuals could use commercial scale manufacturing equipment to produce large quantities of drug products, which could indicate pharmaceutical manufacturing; we are concerned that the Agency may be confusing drug quantity with drug quality. Commercial scale manufacturing and testing equipment can be used to produce and test larger quantities of drug products, but it can also be, and is, used to produce smaller batches of high quality compounded drug products.

The CPG discourages the use of the best manufacturing, and most concerning, the best testing equipment. This restriction is in direct opposition to the profession's move to increase testing of compounded drug products and the use of more analytical equipment. Restrictions on testing will not help the FDA identify manufacturers masquerading as compounders, however, it will limit pharmacists' ability to ensure product safety and quality. In unofficial communications since the release of the CPG, the Agency appears to share pharmacy's view on this point, stating that the Agency does not disagree that commercial scale equipment would help produce a higher quality and safer product. APhA strongly believes that there should be no maximum restrictions on the sophistication of the equipment compounders use – pharmacists should be able and encouraged to use the most advanced equipment available.

The term "commercial scale" is also of concern to the Association. The CPG does not provide a definition of "commercial scale" or provide pharmacists with any threshold that can be used to determine if their equipment qualifies as "commercial scale" and may subject them to possible enforcement action by the Agency. APhA requests that the FDA provide examples of commercial scale equipment and clarify that commercial scale refers to a quantity limitation, not a limitation on the sophistication of the equipment. APhA suggests that the factor be revised and combined with factor 7 which addresses the sale of compounded products to third parties or other entities for resale:

> "Using commercial scale manufacturing equipment to *produce drug products for wholesalers or distributors for resale to other commercial entities.*"

*Factor 7: Compounding drugs for third parties who resell to individual patients or offering compounded products at wholesale to other licensed persons or commercial entities for resale.*[21]

APhA agrees that pharmacists should not sell compounded drug products to wholesalers or distributors for resale. This factor is one of the most appropriate for distinguishing between

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[20] Food and Drug Administration. "Policy." Compliance Policy Guides Manual: Sec. 460.200 Pharmacy Compounding. May 2002. Pg. 4.

[21] Food and Drug Administration. "Policy." Compliance Policy Guides Manual: Sec. 460.200 Pharmacy Compounding. May 2002. Pg. 4.

compounding and manufacturing. Entities that manufacture drug products for resale through commercial channels do not have a close relationship with the prescribing physician or the patient – while the pharmacist/prescriber/patient relationship is the cornerstone of traditional compounding.

APhA, however, is concerned that the factor is overly broad and may restrict compounding pharmacists from two activities: supplying compounded drug products to physicians and hospitals and referring certain prescriptions to another compounding pharmacy. Today, many physicians' offices, hospitals, clinics, and veterinarians turn to their local compounding pharmacist for compounded drug products. The pharmacy supplies the physician's office or hospital with the compounded drug product for use in their office or institution. Although the pharmacy is able to directly bill the patient in a few situations, it is more likely that the physician or other entity will purchase the product from the pharmacy and bill the patient. The CPG should be clarified to state that pharmacists may compound and dispense a drug product for office use, and that the physician's office or hospital may bill the patient for the product.

Additionally, pharmacists occasionally refer prescriptions for compounded drug products to other compounding pharmacies for preparation. A pharmacist may send a prescription for a compounded drug product to another pharmacist because he/she does not feel qualified to prepare the medication, does not have the necessary ingredients or equipment, or does not compound drug products on a regular basis. In these situations, the compounding pharmacist will prepare the drug product and deliver it to the originating pharmacy to dispense to and bill the patient. This allows the patient to obtain all of his/her medications, and keep all of their prescription records on file, at one pharmacy.

APhA is concerned that this factor may deter pharmacists from sending a prescription to a more qualified compounding pharmacist. Not every pharmacist or pharmacy is qualified to compound every possible therapy; therefore pharmacists must be able to refer these prescriptions. Patients are better served by a pharmacist who is qualified, experienced, and practices compounding regularly, not rarely. APhA requests that the Agency further revise this factor to clarify that prescription referrals are allowed.

*Factor 8: Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products. In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular product.*[22]

[22] Food and Drug Administration. "Policy." Compliance Policy Guides Manual: Sec. 460.200 Pharmacy Compounding. May 2002. Pg. 4.

APhA concurs that compounding pharmacists should not regularly produce drug products that are identical to commercially available pharmaceuticals. However, we are concerned that several of the terms included in the factor are not well-defined and leave room for arbitrary interpretation by FDA staff. For example, the factor states that pharmacists should not compound drug products that are "commercially available." What does commercially available mean? Does "commercially available" mean a drug product that a pharmaceutical manufacturer has received FDA approval to produce? Is a product no longer "commercially available" if the product is in short supply? The Agency has stated in unofficial communications that a product cannot be considered commercially available if it cannot be obtained, and that drug shortage compounding is not a violation of the CPG. But this leaves the question of who identifies drug products that qualify for this exception – the FDA or other professional organizations which maintain comprehensive lists of products that are in short supply? The FDA should clarify the CPG to state that drug products may be compounded if the provider is unable to obtain the product.

APhA further requests that the Agency delete the second portion of this factor calling for documentation of medical need. The FDA is not in the position to prospectively or retrospectively approve medical need for compounded drug products. A prescription from a prescriber calling for a compounded drug product should qualify as sufficient proof of medical need. The prescriber is in the best position to determine the appropriate medication for the patient. By inclusion of this requirement, the FDA is attempting to grant itself the unacceptable position as the judge of both medicine and pharmacy practice.

*Factor 9: Failing to operate in conformance with applicable state law regulating the practice of pharmacy.*[23]

APhA agrees that all compounding pharmacists and pharmacies must comply with state laws regulating the practice of pharmacy. We are however, concerned with the FDA's attempt to regulate pharmacy practice. One could presume that inclusion of this factor authorizes FDA to determine whether or not state law is being met. State boards of pharmacy are charged with the development and enforcement of laws regulating pharmacy practice. State pharmacy regulations cover almost every aspect of the profession, from requiring registration of the pharmacy or changing the closing hours of an existing pharmacy to dispensing controlled substances or compounding sterile products.[24]

The majority of state laws regulating pharmacy are completely unrelated to whether a pharmacy is acting as a manufacturer. Examining state regulations such as whether or not a pharmacy has the appropriate type of security system installed[25] or has constructed an adequate enclosure around its prescription department,[26] will not help the FDA distinguish between traditional compounding pharmacies and manufacturers. The Agency should only

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[23] Food and Drug Administration. "Policy." Compliance Policy Guides Manual: Sec. 460.200 Pharmacy Compounding. May 2002. Pg. 4.

[24] Sample taken from the "Regulations of the Virginia Board of Pharmacy." 18 VAC 110-20-10 et seq.

[25] "Regulations of the Virginia Board of Pharmacy." 18 VAC 110-20-180. Security system.

[26] "Regulations of the Virginia Board of Pharmacy." 18 VAC 110-20-190. Prescription department enclosures.

consider violations of state laws that suggest that a manufacturer is masquerading as a pharmacy; and only in conjunction with state regulatory officials. The FDA does not have jurisdiction if it suspects a pharmacy of violating state practice laws. Enforcement of state laws regulating pharmacy is, and should continue to be, a purview of the state boards of pharmacy.

In conclusion, APhA agrees with the FDA that entities with retail pharmacy licenses should not be allowed to operate as pharmaceutical manufacturers under the guise of traditional pharmacy compounding. However, APhA has significant concerns with the 2002 Compliance Policy Guide Manual entitled "Sec. 460.200 Pharmacy Compounding." As discussed in detail in our comments, several of the factors the FDA has identified to distinguish between compounding and manufacturing actually address good compounding practices and safety issues, and have very little to do with the manufacturing of pharmaceuticals. Factors Two (compounding drugs that were withdrawn or removed from the market for safety reasons), Three (compounding from bulk active ingredients that are not components of FDA-approved drugs), Four (receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot has been made in a FDA-approved facility), and Five (receiving, storing, or using drug components not guaranteed or otherwise determined to meet compendia requirements) all address issues related to pharmacy practice. These are inappropriate for the purpose of the CPG and should be deleted.

APhA urges the FDA to reexamine the factors included in the 2002 CPG to distinguish between manufacturing and compounding. As the Agency is aware, regulation of the practice of pharmacy and pharmacy compounding is a function of the state boards of pharmacy. APhA is alarmed that several of the factors concern areas of pharmacy practice that fall within the realm of state regulatory bodies. APhA strongly opposes any attempts by the Agency to utilize the CPG as a means to usurp state authority to regulate pharmacy compounding. APhA requests that the FDA clarify its description of where state regulation ends and FDA involvement begins. The CPG states that:

> "Generally, FDA will continue to defer to state authorities regarding less significant violations of the Act related to pharmacy compounding of human drugs. FDA anticipates that, in such cases, cooperative efforts between the states and the Agency will result in coordinated investigations, referrals, and follow-up actions by the states."[27]

The CPG continues to say that the Agency will consider enforcement action when pharmacists/pharmacies commit "significant violations."[28] This statement seems to imply that state regulatory agencies are only responsible for regulating pharmacy practice when *less* significant violations occur. APhA would like to take this opportunity to remind the

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[27] Food and Drug Administration. "Policy." Compliance Policy Guides Manual: Sec. 460.200 Pharmacy Compounding. May 2002. Pg. 3.
[28] Ibid., Pg. 3.

Agency that state boards of pharmacy are the primary enforcement bodies regulating pharmacy practice, and that any investigation and enforcement action against a pharmacist/pharmacy must be coordinated with the appropriate state board.

Additionally, the FDA should revise the remaining factors to ensure that each factor narrowly targets practices that are clearly indicative of pharmaceutical manufacturing. The current wording of the factors is so vague and ambiguous that they could be manipulated to bring enforcement action against almost any pharmacy. As evidenced by the onslaught of warning letters after the issuance of the 1992 CPG, nebulous factors contained in the guidance document are open to multiple interpretations by FDA inspectors.

As the Agency reviews comments and works to modify the Compliance Policy Guide as appropriate, APhA recommends that the dialogue between the Agency, health care providers, and state regulatory agencies continue.

Thank you for your consideration of the views of the nation's pharmacists. Please contact Susan C. Winckler, APhA's Vice President of Policy and Communications, at 202-429-7533 or swinckler@aphanet.org or Susan K. Bishop, APhA's Manager of Regulatory Affairs and Political Action, at 202-429-7538 or sbishop@aphanet.org with any questions.

Sincerely,

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